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WO 03/022283 A1

(54) Title: COMBINATION OF AN ADENOSINE A2A RECEPTOR ANTAGONIST AND AN ANTIDEPRESSANT OR ANXIOLYTIC

(57) Abstract: This invention relates to a method of treating depression and anxiety-related disorders comprising administering to a mammal in need of such treatment an effective amount of a combination of an adenosine A2A antagonist and an antidepressant or an anxiolytic; another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a combination of an adenosine A2A antagonist and an antidepressant or anxiolytic in a pharmaceutically acceptable carrier.

COMBINATION OF AN ADENOSINE A_{2a} RECEPTOR ANTAGONIST AND AN ANTIDEPRESSANT OR ANXIOLYTIC

BACKGROUND

The present invention relates to a combination of an adenosine A_{2a} receptor antagonist with an antidepressant or an anxiolytic for the treatment of depression or anxiety-related disorders. The invention also relates to pharmaceutical compositions comprising said combinations.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On the central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets.

Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins. Biochemical and pharmacological studies, together with advances in molecular biology, have allowed the identification of at least four subtypes of adenosine receptors: A_1, A_{2a}, A_{2b} and A_3. Agonist activation of A_1 and A_3 receptors is associated with inhibiting the activity of the enzyme adenylate cyclase, whereas activation of A_{2a} and A_{2b} receptors is associated with stimulating the activity of the same enzyme. Analogs of adenosine able to interact as antagonists with the A_1, A_{2a}, A_{2b} and A_3 receptors have also been identified.

Selective antagonists for the A_{2a} receptor are of pharmacological interest because of their reduced level of side effects. In the central nervous system, A_{2a} antagonists can have antidepressant properties and stimulate cognitive functions. Moreover, data has shown that A_{2a} receptors are present in high density in the basal ganglia, known to be important in the control of movement and emotion. Hence, A_{2a} antagonists can improve motor impairment due to neurodegenerative diseases such

as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin.

SUMMARY OF THE INVENTION

This invention relates to a method of treating depression or anxiety-related disorders comprising administering to a mammal in need of such treatment an effective amount of a combination of an adenosine A_{2A} antagonist and an antidepressant or an anxiolytic. In other words, the invention relates to the use of a combination of an adenosine A_{2A} antagonist and an antidepressant or an anxiolytic to treat depression or anxiety-related disorders, or to the use of a combination of an adenosine A_{2A} antagonist and an antidepressant or an anxiolytic for the preparation of a medicament for the treatment of depression or anxiety-related disorders

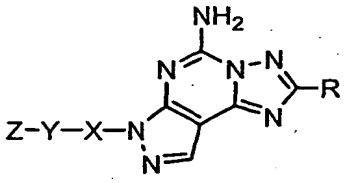
Another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a combination of an adenosine A_{2A} antagonist and an antidepressant in a pharmaceutically acceptable carrier, or a combination of an adenosine A_{2A} antagonist and an anxiolytic in a pharmaceutically acceptable carrier. Alternatively, a pharmaceutical composition comprising an adenosine A_{2A} antagonist and a separate pharmaceutical composition comprising an antidepressant or an anxiolytic can also be administered, simultaneously or sequentially, wherein the adenosine A_{2A} antagonist and the antidepressant or anxiolytic are administered in amounts chosen so that the combination is effective to treat depression or anxiety-related disorders. Kits comprising separate adenosine A_{2A} antagonist and antidepressant or anxiolytic pharmaceutical compositions in a single package are also contemplated.

DETAILED DESCRIPTION

In the present invention, it has been discovered that compounds having adenosine A_{2a} receptor antagonist activity, in combination with antidepressants or anxiolytic agents, are useful in the treatment of depression and anxiety-related disorders. Examples of anxiety-related disorders include social phobias, panic attack, generalized anxiety disorder (GAD), obsessive-compulsive disorders (OCD), and post-traumatic stress disorder (PTSD). The combination of the invention is useful in the treatment of comorbid anxiety and depression in Parkinson's disease.

Suitable adenosine A_{2a} receptor antagonists can be identified by the binding assay described below. Specific examples of suitable adenosine A_{2a} antagonists include the compounds disclosed in several US patents and US and PCT patent applications.

US Serial No. 09/865,071, filed May 24, 2001, equivalent to WO 01/92264, discloses compounds having the structural formula I



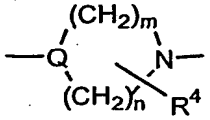
I

or a pharmaceutically acceptable salt thereof, wherein

R is R^1-furanyl, R^1-thienyl, R^1-pyridyl, R^1-pyridyl N-oxide, R^1-oxazolyl, R^{10}-phenyl, R^1-pyrrolyl or C_4-C_6 cycloalkenyl;

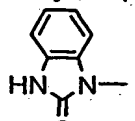
X is C_2-C_6 alkylene or $-C(O)CH_2$-;

Y is $-N(R^2)CH_2CH_2N(R^3)$-, $-OCH_2CH_2N(R^2)$-, -O-, -S-, $-CH_2S$-, $-(CH_2)_2-NH$-, or



and

Z is R^5-phenyl, R^5-phenyl(C_1-C_6)alkyl, R^5-heteroaryl, diphenylmethyl, R^6-C(O)-, R^6-SO_2-, R^6-OC(O)-, R^7-N(R^8)-C(O)-, R^7-N(R^8)-C(S)-,

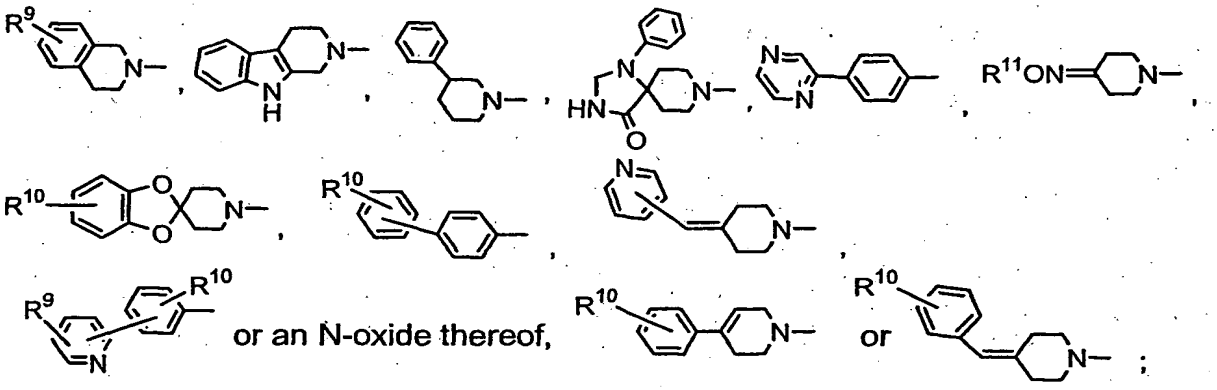


, phenyl-CH(OH)-, or

phenyl-C(=NOR^2)-; or when Q is , Z is also phenylamino or pyridylamino;

or

Z and Y together are



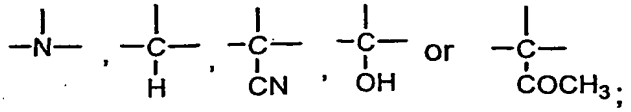
or an N-oxide thereof,

R^1 is 1 to 3 substituents independently selected from hydrogen, C_1-C_6-alkyl, $-CF_3$, halogen, $-NO_2$, $-NR^{12}R^{13}$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, and C_1-C_6 alkylsulfonyl;

R^2 and R^3 are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

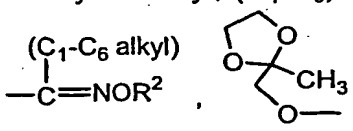
m and n are independently 2-3;

Q is



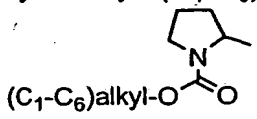
R^4 is 1-2 substituents independently selected from the group consisting of hydrogen and C_1-C_6alkyl, or two R^4 substituents on the same carbon can form =O;

R^5 is 1 to 5 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, -CN, di-((C_1-C_6)alkyl)amino, $-CF_3$, $-OCF_3$, acetyl, $-NO_2$, hydroxy(C_1-C_6)alkoxy, (C_1-C_6)-alkoxy(C_1-C_6)alkoxy, di-((C_1-C_6)-alkoxy)(C_1-C_6)alkoxy, (C_1-C_6)-alkoxy(C_1-C_6)alkoxy-(C_1-C_6)-alkoxy, carboxy(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxycarbonyl(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl(C_1-C_6)alkoxy, di-((C_1-C_6)alkyl)amino(C_1-C_6)alkoxy, morpholinyl, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO-(C_1-C_6)alkoxy, tetrahydropyranyloxy, (C_1-C_6)alkylcarbonyl(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy(C_1-C_6)-alkoxy, $-SO_2NH_2$, phenoxy,



; or adjacent R^5 substituents together are $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, $-O-CF_2-O-$ or $-O-CF_2CF_2-O-$ and form a ring with the carbon atoms to which they are attached;

R^6 is (C_1-C_6)alkyl, R^5-phenyl, R^5-phenyl(C_1-C_6)alkyl, thienyl, pyridyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)alkyl-OC(O)-NH-(C_1-C_6)alkyl-, di-((C_1-C_6)alkyl)aminomethyl, or



;

R^7 is (C_1-C_6)alkyl, R^5-phenyl or R^5-phenyl(C_1-C_6)alkyl;

R^8 is hydrogen or C_1-C_6 alkyl; or R^7 and R^8 together are $-(CH_2)_p$-A-$(CH_2)_q$, wherein p and q are independently 2 or 3 and A is a bond, $-CH_2$-, -S- or -O-, and form a ring with the nitrogen to which they are attached;

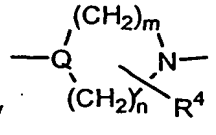
R^9 is 1-2 groups independently selected from hydrogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, halogen, $-CF_3$ and (C_1-C_6)alkoxy(C_1-C_6)alkoxy ;

R^{10} is 1 to 5 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, -CN, $-NH_2$, C_1-C_6alkylamino, di-((C_1-C_6)alkyl)amino, $-CF_3$, $-OCF_3$ and $-S(O)_{0-2}$(C_1-C_6)alkyl;

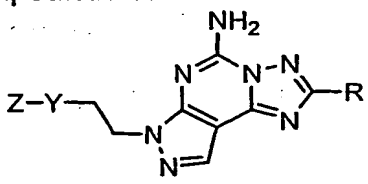
R^{11} is H, C_1-C_6 alkyl, phenyl, benzyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, di-((C_1-C_6)alkyl)amino(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl or piperidino(C_1-C_6)alkyl;

R^{12} is H or C_1-C_6 alkyl; and

R^{13} is (C_1-C_6)alkyl-C(O)- or (C_1-C_6)alkyl-SO_2-.

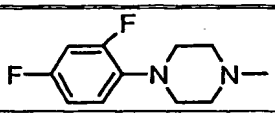
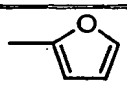
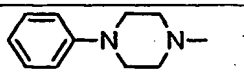
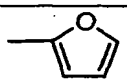
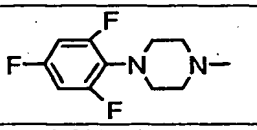
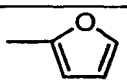
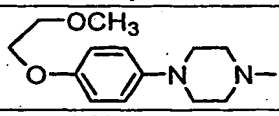
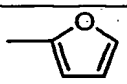
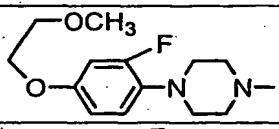
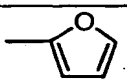
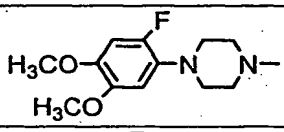
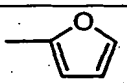
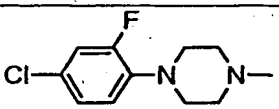
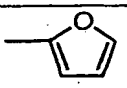
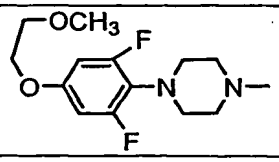
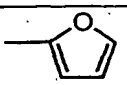
Preferred compounds of formula I are those wherein R is R^1-furanyl, R^1-thienyl, R^1-pyrrolyl or R^{10}-phenyl, more preferably R^1-furanyl. R^1 is preferably hydrogen or halogen. Another group of preferred compounds is that wherein X is alkylene, preferably ethylene. Y is preferably  wherein Q is  or , with Q preferably being nitrogen. Preferably, m and n are each 2, and R^4 is H. A preferred definition for Z is R^5-phenyl, R^5-heteroaryl, R^6-C(O)- or R^6-SO_2-. R^5 is preferably H, halogen, alkyl, alkoxy, hydroxyalkoxy or alkoxyalkoxy. R^6 is preferably R^5-phenyl.

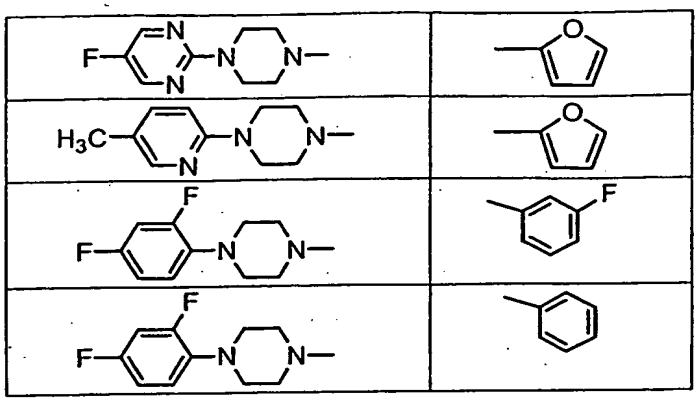
Preferred specific compounds of formula I are those of the formula IA



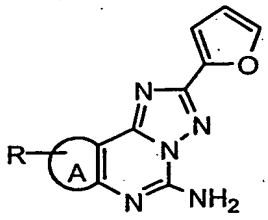
IA

wherein R and Z-Y are as defined in the following table:

Z-Y-	R
	
	
	
	
	
	
	
	



Other useful adenosine A_{2a} receptor antagonists include those disclosed in WO 95/01356 as compounds having the structural formula II



II

wherein:

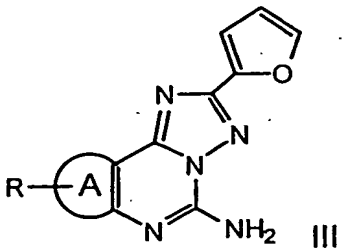
A is pyrazole, imidazole or a triazole ring;

R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl; C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with one or more halogen atoms, hydroxy groups, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$; aryl optionally substituted with halogen atoms, C_1-C_4 alkoxy groups, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxyamido; C_7-C_{10} aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula $-(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer from 1 to 5;

R_1, R_2 which are the same or different, are hydrogen, C_1-C_5 alkyl, C_7-C_{10} aralkyl, phenyl, or taken together with the nitrogen they are linked to, form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms such as N, O, S and n is an integer from 2 to 5.

Preferably, compounds of formula II are those wherein R is hydrogen, C_1-C_8 alkyl, aryl or C_7-C_{10} aralkyl optionally substituted, preferably with halogen atoms.

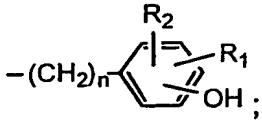
US 5,935,964 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formula III



III

wherein A is pyrazole, imidazole or triazole ring;

R is

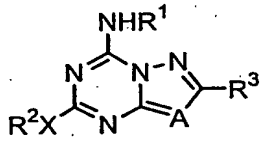


R_1 and R_2, which are the same or different, are H, OH, halogen, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy or carboxamido; or the OH group, together with one of R_1 or R_2, or R_1 and R_2, can form a methylenedioxy group –O-CH_2-O-; and

n is an integer from 0-4.

Preferred compounds of formula III are those wherein A is pyrazolo[4,3-e] or 1,2,3-triazolo[5,4-e].

US 5,565,460 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formulas IVA and IVB, wherein formula IVA is



IVA

wherein R^1 represents hydrogen, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower alkanoyl;

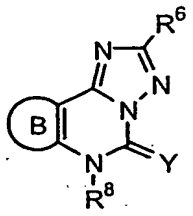
R^2 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group;

R^3 represents a substituted or unsubstituted heterocyclic group;

X represents a single bond, O, S, S(O), $S(O)_2$, or NR^4 (in which R^4 represents hydrogen, or substituted or unsubstituted lower alkyl; or R^2 and NR^4 are combined to form a substituted or unsubstituted 4 to 6-membered saturated heterocyclic group): and

A represents N or CR^5 (in which R^5 represents hydrogen, or a substituted or unsubstituted lower alkyl); and

wherein formula IVB is



IVB

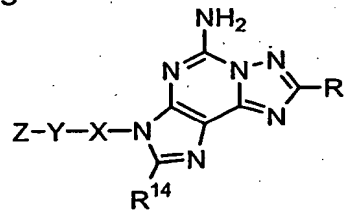
wherein R^6 represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group;

Y represents O, S, or NR^7 (in which R^7 represents substituted or unsubstituted lower alkyl, substituted or unubstituted cycloalkyl, or substituted or unsubstituted aryl);

R^8 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group; and

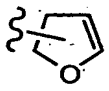
B and the adjacent two carbon atoms are combined to form a substituted or unsubstituted, partially saturated or unsaturated, monocyclic or bicyclic, carbocyclic or heterocyclic group.

US Provisional Application 60/329,567 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formula V

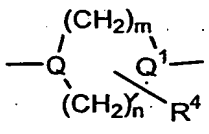


V

or a pharmaceutically acceptable salt thereof, wherein

R is R^1-heteroaryl, R^{10}-phenyl, C_4-C_6 cycloalkenyl, $-C(=CH_2)CH_3$, $-C\equiv C-CH_3$, $-CH=C(CH_3)_2$,  or  ;

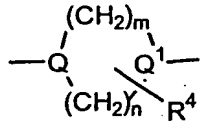
X is C_1-C_6 alkylene, $-C(O)CH_2-$ or $-C(O)N(R^2)CH_2-$;

Y is $-N(R^2)CH_2CH_2N(R^3)-$, $-OCH_2CH_2N(R^2)-$, -O-, -S-, $-CH_2S-$, $-(CH_2)_{2-3}-N(R^2)-$, R^5-divalent heteroaryl,  ,  or 

and

Z is R^5-phenyl, R^5-phenyl(C_1-C_6)alkyl, R^5-heteroaryl, R^5-bicyclic heteroaryl, R^5-benzofused heteroaryl, diphenylmethyl or R^6-C(O)-;

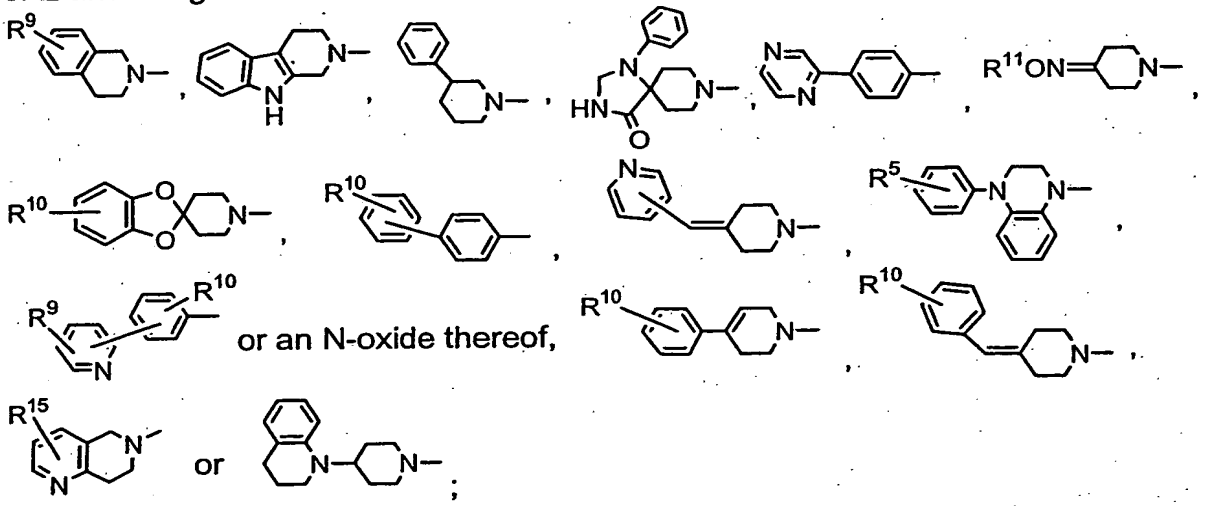
or when Y is



Z is also R^6-SO_2-, R^7-N(R^8)-C(O)- or R^7-N(R^8)-C(S)-;

or when Q is , Z is also phenylamino or pyridylamino;

or Z and Y together are



or an N-oxide thereof,

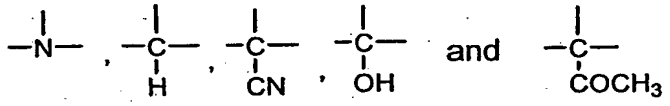
R^1 is 1 to 3 substituents independently selected from hydrogen, C_1-C_6-alkyl, -CF_3, halogen, –NO_2, –$NR^{12}R^{13}$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, -$COOR^7$ or –$C(O)NR^2R^3$;

R^2 and R^3 are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

m and n are independently 2-3;

p and q are independently 0-2;

Q and Q^1 are independently selected from the group consisting of

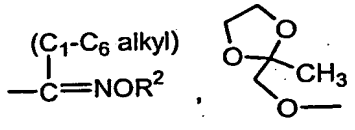


provided that one of Q and Q^1 is  ;

R^4 is 1-2 substituents independently selected from the group consisting of hydrogen, C_1-C_6alkyl, R^1-aryl and R^1-heteroaryl, or two R^4 substituents on the same carbon can form =O;

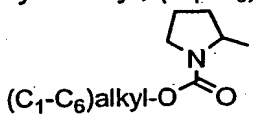
R^5 is 1 to 5 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, -CN, di-((C_1-C_6)alkyl)amino, -CF_3, -OCF_3, acetyl, -NO_2, hydroxy(C_1-C_6)alkoxy, (C_1-C_6)-alkoxy(C_1-C_6)alkoxy, di-((C_1-C_6)-alkoxy)(C_1-C_6)alkoxy, (C_1-C_6)-alkoxy(C_1-C_6)alkoxy-(C_1-C_6)-alkoxy, carboxy(C_1-C_6)-

alkoxy, (C_1-C_6)-alkoxycarbonyl(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl(C_1-C_6)alkoxy, di-((C_1-C_6)alkyl)amino(C_1-C_6)alkoxy, morpholinyl, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO_2-(C_1-C_6)alkoxy, tetrahydropyranyloxy, (C_1-C_6)alkylcarbonyl(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy(C_1-C_6)-alkoxy, $-SO_2NH_2$, phenoxy,



, $(R^2O)_2$-P(O)-CH_2-O- and $(R^2O)_2$-P(O)-; or adjacent R^5 substituents together are –O-CH_2-O-, -O-CH_2CH_2-O-, –O-CF_2-O- or -O-CF_2CF_2-O- and form a ring with the carbon atoms to which they are attached;

R^6 is (C_1-C_6)alkyl, R^5-phenyl, R^5-phenyl(C_1-C_6)alkyl, thienyl, pyridyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)alkyl-OC(O)-NH-(C_1-C_6)alkyl-, di-((C_1-C_6)alkyl)aminomethyl, or



;

R^7 is (C_1-C_6)alkyl, R^5-phenyl or R^5-phenyl(C_1-C_6)alkyl;

R^8 is hydrogen or C_1-C_6 alkyl; or R^7 and R^8 together are $-(CH_2)_p$-A-$(CH_2)_q$, wherein p and q are independently 2 or 3 and A is a bond, $-CH_2$-, -S- or –O-, and form a ring with the nitrogen to which they are attached;

R^9 is 1-2 substituents independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, halogen, $-CF_3$ and (C_1-C_6)alkoxy-(C_1-C_6)alkoxy;

R^{10} is 1 to 5 substituents independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, -CN, $-NH_2$, C_1-C_6alkylamino, di-((C_1-C_6)alkyl)amino, $-CF_3$, $-OCF_3$, $-S(O)_{0-2}$(C_1-C_6)alkyl and $-CH_2$-SO_2-phenyl;

R^{11} is H, C_1-C_6 alkyl, phenyl, benzyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, di-((C_1-C_6)alkyl)amino(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl or piperidino(C_1-C_6)alkyl;

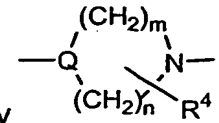
R^{12} is H or C_1-C_6 alkyl;

R^{13} is H, (C_1-C_6)alkyl-C(O)- or (C_1-C_6)alkyl-SO_2-;

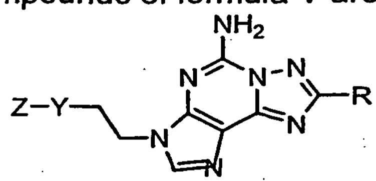
R^{14} is H, halogen, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl or NR^2R^3-(C_1-C_6)alkyl; and

R^{15} is H, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy.

Preferred compounds of formula V are those wherein R is R^1-furanyl, R^1-thienyl, R^1-pyrrolyl, R^1-pyridyl or R^{10}-phenyl, more preferably R^1-furanyl or R^{10}-phenyl. R^1 is preferably hydrogen or halogen. R^{10} is preferably hydrogen, halogen, alkyl or –CF_3. Another group of preferred compounds is that wherein X is alkylene, preferably

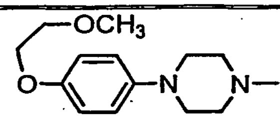
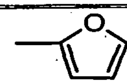
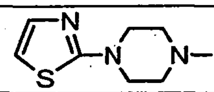
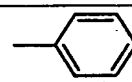
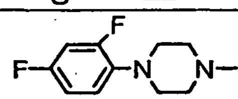
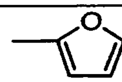
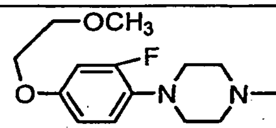
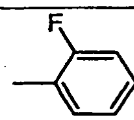
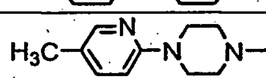
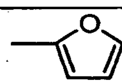
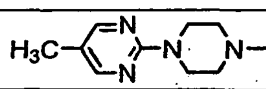
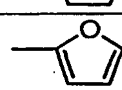
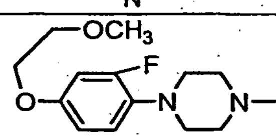
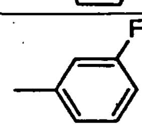
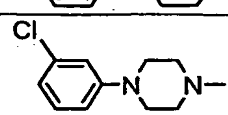
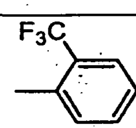
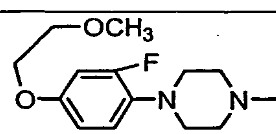
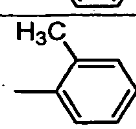
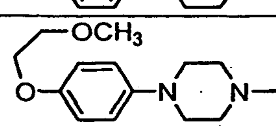
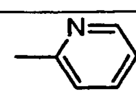
ethylene. Y is preferably  wherein Q is $-\overset{|}{N}-$ or $-\overset{|}{C}H-$, with Q preferably being nitrogen. Preferably, m and n are each 2, and R^4 is H. A preferred definition for Z is R^5-phenyl or R^5-heteroaryl. R^5 is preferably H, halogen, alkyl, alkoxy, hydroxyalkoxy or alkoxyalkoxy. R^6 is preferably R^5-phenyl.

Preferred specific compounds of formula V are those of the formula VA

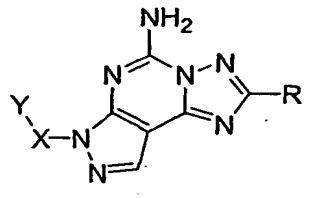


VA

wherein R and Z-Y are as defined in the following table:

Z-Y-	R
	
	
	
	
	
	
	
	
	
	

US Provisional Application 60/334,342 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formula VI



VI

or pharmaceutically acceptable salts thereof, wherein

R is R^1-furanyl, R^1-thienyl, R^1-pyridyl, R^1-oxazolyl, R^1-pyrrolyl or R^2-phenyl;

X is $-(CH_2)_n-$;

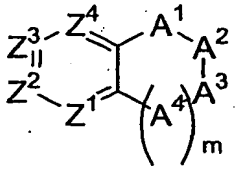
Y is a piperidinyl or pyrrolidinyl group fused to a monocyclic or bicyclic aryl or heteroaryl wherein X is attached to the N atom of the piperidinyl or pyrrolidinyl group;

n is an integer from 1 to 4;

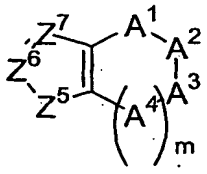
R^1 is 1-3 substituents, which may be the same or different, and are independently selected from hydrogen, C_1-C_6-alkyl, $-CF_3$, halogen or NO_2; and

R^2 is 1-3 substituents, which may be the same or different, and are independently selected from hydrogen, C_1-C_6-alkyl, $-CF_3$, halogen, NO_2, C_1-C_6-alkoxy, C_1-C_6-acyloxy, C_1-C_6-alkylamino, C_1-C_6-acylamino, C_1-C_6-alkylsulfonamido, C_1-C_6-alkylaminosulfonyl, C_1-C_6-dialkylaminosulfonyl, aminosulfonyl, or hydroxyl.

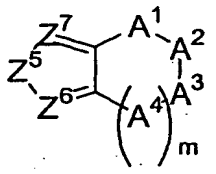
In a preferred embodiment of compounds of formula VI, Y is



or



or



wherein A^1 is N-X, and A^2 and A^3 each are CR^4R^5, or

A^1 and A^3 each are CR^4R^5, and A^2 is N-X, or

A^1 and A^2 each are CR^4R^5, and A^3 is N-X;

A^4 is CR^4R^5;

Z^1, Z^2, Z^3 and Z^4 are selected from the group consisting of N and CR^3, provided that 0-2 of Z^1, Z^2, Z^3 or Z^4 are N and the remainder are CR^3;

Z^5 is NR^5, O, S or CR^4R^5;

Z^6 is N or CR^3;

Z^7 is N or CR^3;

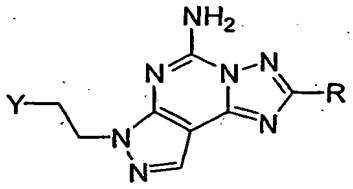
m is an integer from 0 to 2;

R^3 is hydrogen, C_1-C_6-alkyl, CF_3, halogen, NO_2, C_1-C_6-alkoxy, C_1-C_6-acyloxy, C_1-C_6-alkylamino, C_1-C_6-acylamino, C_1-C_6-alkylsulfonamino, C_1-C_6-alkylaminosulfonyl, C_1-C_6-dialkylaminosulfonyl, aminosulfonyl, or hydroxyl;

R^4 is hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, -CF_3, halogen, hydroxy, or NO_2; and

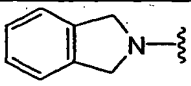
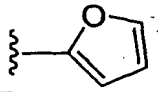
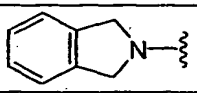
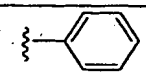
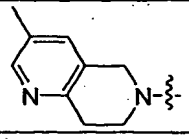
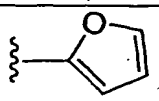
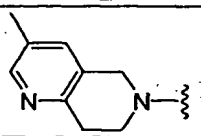
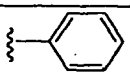
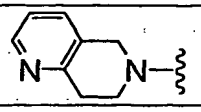
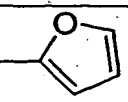
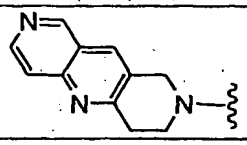
R^5 is hydrogen or C_1-C_6 alkyl.

Preferred specific examples of compounds of formula VI include compounds of the formula VIA

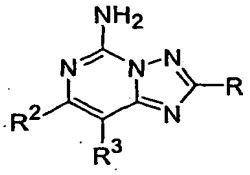


VIA

wherein Y and R are defined in the following table:

Y	R
	
	
	
	
	
	

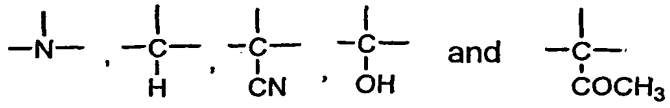
US Provisional Application 60/334,293 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formula VII



VII

or pharmaceutically acceptable salts thereof, wherein

Q and Q^1 may be the same or different and are independently selected from the group consisting of



provided that one of Q and Q^1 is  ;

m and n are independently 1-3;

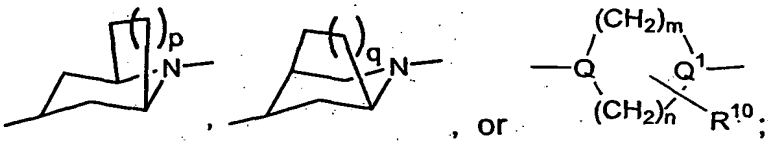
p and q are independently 0-2;

W is aryl or heteroaryl having 1-3 heteroatoms, which may be the same or different and are independently selected from N, O or S, said aryl or heteroaryl optionally substituted by 1-3 substituents, which may be the same or different and are independently selected from alkyl, halo, hydroxy, hydroxyalkyl, alkoxy, $-NR^6R^7$, $(C_2$-$C_6)$alkene, or -CN;

X is H, NH_2, $-N(R^6)(CH_2)_m-C_6H_5$, $-N(R^6)(CH_2)_{m+1}-OH$, $-N(CH_3)_2$, or

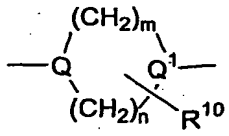
X is R^{18} which is attached to -Y-Z;

Y is $-N(R^6)CH_2CH_2N(R^7)-$, $-OCH_2CH_2N(R^6)-$, -O-, -S-, $-CH_2S-$, $-(CH_2)_{2-3}-N(R^6)-$, R^8-divalent heteroaryl,

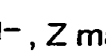


Z is alkoxyalkyl, R^8-phenyl, R^8-phenyl$(C_1$-$C_6)$alkyl, R^8-heteroaryl, R^8-bicyclic heteroaryl; R^8-benzofused heteroaryl, diphenylmethyl or R^9-C(O)-; or

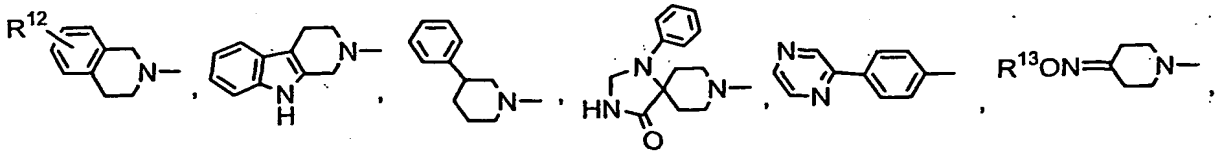
when Y is

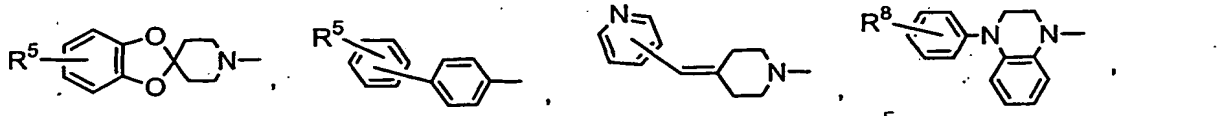


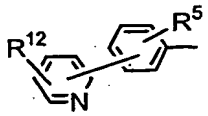
Z may also be H, R^9-SO_2-, $R^{17}-N(R^{11})-C(O)-$ or $R^{17}-N(R^{11})-C(S)-$; or

when Q is  , Z may also be phenylamino or pyridylamino; or

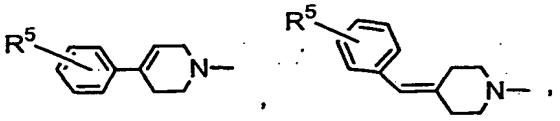
Z and Y taken together are

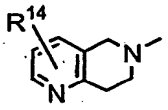




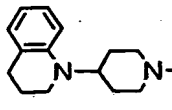


or an N-oxide thereof,



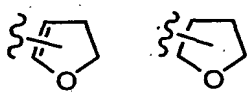


or



;

R is R^4-heteroaryl, R^5-phenyl, $(C_4\text{-}C_6)$cycloalkenyl, $-C(=CH_2)CH_3$, $-C\equiv C\text{-}CH_3$,



, $-CH=C(CH_3)_2$, or $-CH=CH\text{-}CH_3$;

R^2 is halo, -W-X, $-NH(CH_2)_m$-W-X, $-NHCH(CH_3)$-W-X, or

R^2 is alkyl, alkenyl or $-NR^{18}R^{19}$ which is optionally substituted by -W-X;

R^3 is H, halo, alkyl, trifluoromethyl, alkoxy, alkoxyalkyl, hydroxyalkyl, alkylamino, alkylaminoalkyl, dialkylamino, dialkylaminoalkyl, aminoalkyl, aryl, heteroaryl, or CN;

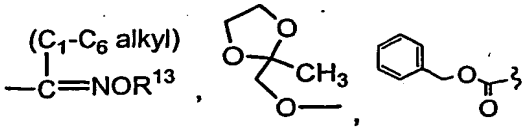
R^4 is 1 to 3 substituents, which may be the same or different and are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$-alkyl, $-CF_3$, halogen, $-NO_2$, $-NR^{15}R^{16}$, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $-COOR^{17}$ or $-C(O)NR^6R^7$;

R^5 is 1 to 5 substituents, which may be the same or different and are independently selected from the group consisting of hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, -CN, $-NH_2$, $(C_1\text{-}C_6)$alkylamino, di-$((C_1\text{-}C_6)$alkyl)amino, $-CF_3$, $-OCF_3$, $-S(O)_{0\text{-}2}(C_1\text{-}C_6)$alkyl and $-CH_2\text{-}SO_2$-phenyl;

R^6 and R^7, which may be the same or different, are independently selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl;

R^8 is 1 to 5 substituents, which may be the same or different and are independently selected from the group consisting of hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, hydroxy, $C_1\text{-}C_6$ alkoxy, -CN, amino, di-$((C_1\text{-}C_6)$alkyl)amino, $-CF_3$, $-OCF_3$, acetyl, $-NO_2$,

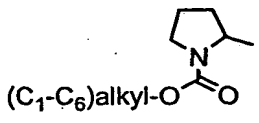
hydroxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxyhydroxy, (C_1-C_6)-alkoxy(C_1-C_6)alkoxy, di-((C_1-C_6)-alkoxy)(C_1-C_6)alkoxy, (C_1-C_6)-alkoxy(C_1-C_6)alkoxy-(C_1-C_6)-alkoxy, carboxy(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxycarbonyl(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl(C_1-C_6)alkoxy, di-((C_1-C_6)alkyl)amino(C_1-C_6)alkoxy, morpholinyl, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO_2-(C_1-C_6)alkoxy, tetrahydropyranyloxy, (C_1-C_6)alkylcarbonyl(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy(C_1-C_6)-alkoxy, -SO_2NH_2, phenoxy,



, -O-CH_2-P(O)(OR^6)$_2$,- and –P(O)(OR^6)$_2$; or

adjacent R^8 *substituents together are* –O-CH_2-O-, -O-CH_2CH_2-O-, –O-CF_2-O- or -O-CF_2CF_2-O- and form a ring with the carbon atoms to which they are attached;

R^9 is (C_1-C_6)alkyl, R^8-phenyl, R^8-phenyl(C_1-C_6)alkyl, thienyl, pyridyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)alkyl-OC(O)-NH-(C_1-C_6)alkyl-, di-((C_1-C_6)alkyl)aminomethyl, or



;

R^{10} is 1-2 substituents, which may be the same or different and are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, R^5-aryl and R^4-heteroaryl, or two R^{10} substituents on the same carbon can form =O;

R^{11} is hydrogen or (C_1-C_6)alkyl; or R^{17} and R^{11} taken together are –(CH_2)$_p$-A-(CH_2)$_q$, wherein p and q are independently 2 or 3 and A is a bond, –CH_2-, -S- or –O-, and form a ring with the nitrogen to which they are attached;

R^{12} is 1-2 substituents, which may be the same or different and are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, halogen, and -CF_3;

R^{13} is H, (C_1-C_6)alkyl, phenyl, benzyl, (C_2-C_6)alkenyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, di-((C_1-C_6)alkyl)amino(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl or piperidino(C_1-C_6)alkyl;

R^{14} is H, halogen, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

R^{15} is H or (C_1-C_6)alkyl;

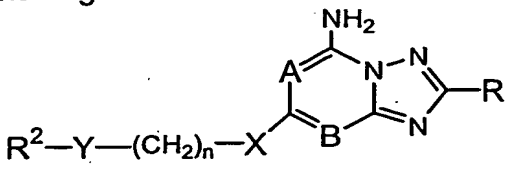
R^{16} is H, (C_1-C_6)alkyl-C(O)- or (C_1-C_6)alkyl-SO_2-;

R^{17} is (C_1-C_6)alkyl, R^8-phenyl or R^8-phenyl(C_1-C_6)alkyl;

R^{18} is a bond, -CH_2-, -CH(OH)-, -$CH(CH_3)$-, or -$C(CH_3)_2$-; and

R^{19} is H or lower alkyl.

US Provisional Application 60/334,385 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formula VIII



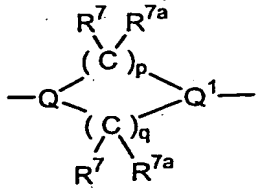
VIII

wherein:

A is $C(R^1)$ and B is $C(R^{1a})$; or A is $C(R^1)$ and B is N; or A is N and B is $C(R^{1a})$; or A and B are both N;

R^1 and R^{1a} are independently selected from the group consisting of H, (C_1-C_6)-alkyl, halo, CN and $-CF_3$;

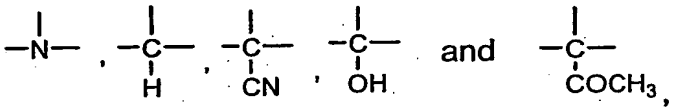
Y is –O-, -S-, -SO-, $-SO_2-$, R^5-heteroaryldiyl, R^5-arylene or



;

p and q are independently 2-3;

Q and Q^1 are independently selected from the group consisting of



provided that at least one of Q and Q^1 is  ;

n is 1, 2 or 3; and

(a) A and B are both N, and X is $-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, $-N(R^9)-$, R^4-arylene or R^4-heteroaryldiyl; or A and B are both N, Y is a bond and X is –C(O)-, R^4-arylene or R^4-heteroaryldiyl; or

(b) A is $C(R^1)$, B is N, and X is $-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, $-N(R^9)-$, R^4-arylene or R^4-heteroaryldiyl; or A is $C(R^1)$, B is N, Y is a bond, and X is –C(O)- or R^4-heteroaryldiyl; or

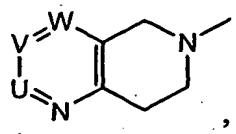
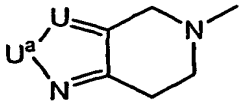
(c) A is $C(R^1)$, B is $C(R^{1a})$, and X is $-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, R^4-arylene, R^4-heteroaryldiyl, or $-N(R^9)-$, provided that when X is $-N(R^9)-$, R^2-Y is not aryl(C_1-C_6alkyl)arylene; or A is $C(R^1)$, B is $C(R^{1a})$, Y is a bond, and X is $-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, R^4-arylene, $-N(R^9)-$ or R^4-heteroaryldiyl, provided that when X is $-N(R^9)-$ or R^4-heteroaryldiyl, R^2 is not phenyl or phenyl(C_1-C_6)alkyl;

or n is 2 or 3; and

(d) A is N, B is $C(R^{1a})$, and X is $-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, $-N(R^9)-$, R^4-arylene or R^4-heteroaryldiyl; or A is N, B is $C(R^{1a})$, Y is a bond and X is -C(O)-, $-N(R^9)-$, R^4-arylene or R^4-heteroaryldiyl;

R is R^5-aryl, R^5-heteroaryl, R^6-(C_2-C_6)alkenyl or R^6-(C_2-C_6)alkynyl;

R^2 is R^5-aryl, R^5-heteroaryl, R^5-aryl(C_1-C_6)alkyl or R^5-heteroaryl(C_1-C_6)alkyl; or R^2-Y is selected from the group consisting of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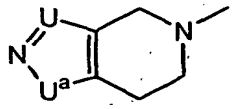

;

U, V, and W are independently selected from the group consisting of N and CR^1, provided that at least one of U, V and W is CR^1;

U^a is –O-, -S-, -NH-, or $-N(C_1$-C_6 alkyl)-;

R^3 and R^{3a} are independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl and di(C_1-C_6)alkylamino(C_1-C_6)alkyl;

R^4 is 1-3 substituents selected from the group consisting of H, (C_1-C_6)alkyl, -OH, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo, $-CF_3$, and –CN;

R^5 is 1-3 substituents independently selected from the group consisting of H, (C_1-C_6)alkyl, -OH, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy, halo, $-CF_3$, -CN, $-NH_2$, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, amino(C_1-C_6)-alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkanoyl-amino, (C_1-C_6)alkanesulfonylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkylthio(C_1-C_6)alkyl, R^6-(C_2-C_6)alkenyl and R^6-(C_2-C_6)alkynyl;

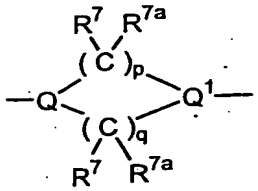
R^6 is 1 to 3 substituents independently selected from the group consisting of H, (C_1-C_6)alkyl, -OH, (C_1-C_6)alkoxy and halo;

R^7 and R^{7a} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, R^8-aryl and R^8-heteroaryl, or an R^7 and an R^{7a} substituent on the same carbon can form =O;

R^8 is 1 to 3 substituents independently selected from H, (C_1-C_6)alkyl, -OH, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo, $-CF_3$, and –CN; and

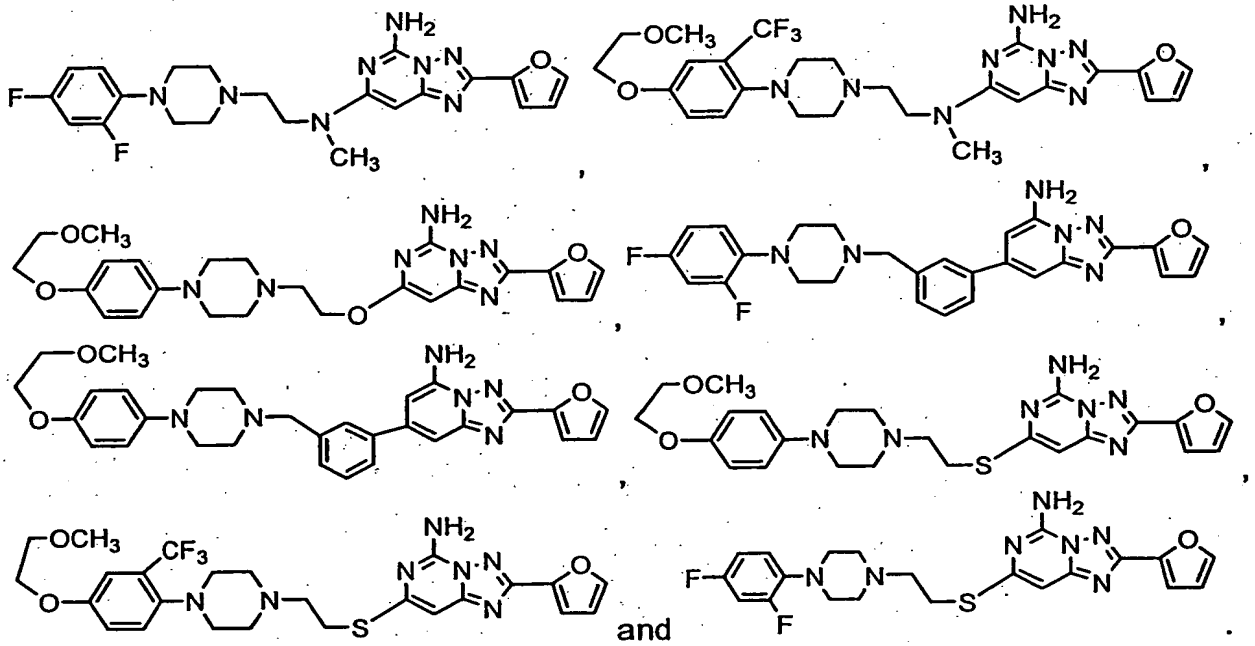
R^9 is H, C_1-C_6 alkyl, hydroxy(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_2-C_6)alkyl, amino(C_2-C_6)alkyl, (C_1-C_6)alkylamino(C_2-C_6)alkyl and di(C_1-C_6)alkylamino(C_2-C_6)alkyl.

Preferred compounds of formula VIII are those wherein A is N or C(R^1) and B is C(R^{1a}), with compounds wherein A is N and B is C(R^{1a}) being more preferred. Another group of preferred compounds is that wherein X is –O-, -S-, -N(R^9)- or R^4-arylene. Preferred definitions for Y are a bond or piperazinyl (i.e., a group of the formula



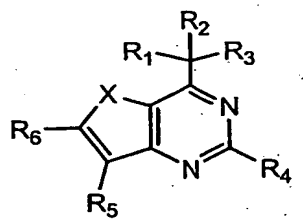
wherein Q and Q^1 are each nitrogen, p and q are each 2, and each R^7 and each R^{7a} is H). R^2 is preferably R^5-aryl. R is preferably furyl.

Preferred specific examples of compounds of formula VIII include compounds of the formula



and

WO 01/02409 discloses useful adenosine A_{2a} receptor antagonist compounds having the structural formula IX



IX

wherein

X is O or S;

R_1 and R_2 are independently selected from hydrogen, alkyl, aryl, hydroxy, alkoky, aryloxy, cyano, nitro, CO_2R_7, COR_7, $OCOR_7$, $CONR_7R_8$, $CONR_7NR_8R_9$, $OCONR_7R_8$, NR_7R_8, NR_7COR_8, $NR_7CONR_8R_9$, $NR_7CO_2R_8$, $NR_7SO_2R_8$, $NR_7CONR_8NR_9R_{10}$, $NR_7NR_8CO_2R_9$, $NR_7NR_8CONR_9R_{10}$, $NR_7SO_2NR_8R_9$, SO_2R_7, SOR_7, SR_7 and $SO_2NR_7R_8$, or $R_1$and R_2 together form a carbonyl group (C=O), an oxime group ($C=NOR_{11}$), an imine group ($C=NR_{11}$) or a hydrazine group ($C=NNR_{11}R_{12}$), or $R_1$and R_2 together form a 5, 6 or 7 membered carbocyclic or heterocyclic ring;

R_3 is alkyl or aryl;

R_4, R_5 and R_6 ate independently selected from hydrogen, alkyl, aryl, halogen, hydroxy, nitro, cyano, alkoxy, aryloxy, CO_2R_7, COR_7, $OCOR_7$, SO_2R_7, SOR_7, SR_7, $SO_2NR_7R_8$, , $CONR_7R_8$, $CONR_7NR_8R_9$, $OCONR_7R_8$, NR_7R_8, NR_7COR_8, $NR_7CONR_8R_9$, $NR_7CO_2R_8$, $NR_7SO_2R_8$, $CR_7=NOR_8$, $NR_7CONR_8NR_9R_{10}$, $NR_7NR_8CO_2R_9$, $NR_7NR_8CONR_9R_{10}$, $SO_2NR_7NR_8R_9$, $NR_7SO_2NR_8R_9$, $NR_7NR_8SO_2R_9$, $NR_7NR_8CO_2R_9$, $NR_7NR_8R_9$ and $NR_7CSNR_8R_9$, or R_5 and R_6 together form a 5, 6 or 7 membered carbocyclic or heterocyclic ring; and

R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from hydrogen, alkyl and aryl, or a pharmaceutically acceptable salt or prodrug thereof.

Agents known to be useful in the treatment of depression ("antidepressants") which can be administered in combination with an adenosine A_{2a} receptor antagonist include: selective serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, citalopram, mirtazepine and fluvoxamine; selective norepinephrine reuptake inhibitors such as reboxetine, desipramine, amitriptyline, nortriptyline and imipramine; mixed serotonin/ norepinephrine reuptake inhibitors such as venlafaxine, buproprion, nefazodone and milnacipran, and combinations thereof.

Agents known to be useful in the treatment of anxiety-related disorders (i.e., anxiolytics) which can be administered in combination with an adenosine A_{2a} receptor antagonist include alprazolam, buspirone, lorazepam, diazepam, clonazepam, doxepin, chlordiazepoxide and meprobamate, and combinations thereof.

The US patents and applications cited herein are incorporated herein by reference. The adenosine A_{2a} receptor antagonists are prepared by known methods as described in the cited patents and applications. The antidepressants and anxiolytics are commercially available and are described in the literature, e.g., in The Physicians' Desk Reference (Montvale: Medical Economics Co., Inc., 2001)

It is contemplated that two or more A_{2a} receptor antagonists could be administered in combination with one or more antidepressants or one or more

anxiolytics to treat depression or anxiety-related disorders; it is also contemplated that one or more antidepressants and one or more anxiolytics could be combined with one or more A_{2a} receptor antagonists for the treatment of depression or anxiety-related disorders.

The pharmacological activity of the compounds of the invention was determined by the following *in vitro* and *in vivo* assays to measure A_{2a} receptor activity.

Human Adenosine A_{2a} and A_1 Receptor Competition Binding Assay Protocol

Membrane sources:

A_{2a}: Human A_{2a} Adenosine Receptor membranes, Catalog #RB-HA2a, Receptor Biology, Inc., Beltsville, MD. Dilute to 17 µg/100 µl in membrane dilution buffer (see below).

Assay Buffers:

Membrane dilution buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM $MgCl_2$.

Compound Dilution Buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM $MgCl_2$ supplemented with 1.6 mg/ml methyl cellulose and 16% DMSO. Prepared fresh daily.

Ligands:

A_{2a}: [3H]-SCH 58261, custom synthesis, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 1 nM in membrane dilution buffer. Final assay concentration is 0.5 nM.

A_1: [3H]- DPCPX, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 2 nM in membrane dilution buffer. Final assay concentration is 1 nM.

Non-specific Binding:

A_{2a}: To determine non-specific binding, add 100 nM CGS 15923 (RBI, Natick, MA). Working stock is prepared at 400 nM in compound dilution buffer.

A_1: To determine non-specific binding, add 100 µM NECA (RBI, Natick, MA). Working stock is prepared at 400 µM in compound dilution buffer.

Compound Dilution:

Prepare 1 mM stock solutions of compounds in 100% DMSO. Dilute in compound dilution buffer. Test at 10 concentrations ranging from 3 µM to 30 pM. Prepare working solutions at 4X final concentration in compound dilution buffer.

Assay procedure:

Perform assays in deep well 96 well plates. Total assay volume is 200 µl. Add 50 µl compound dilution buffer (total ligand binding) or 50 µl CGS 15923 working solution (A_{2a} non-specific binding) or 50 µl NECA working solution (A_1 non-specific binding) or 50 µl of drug working solution. Add 50 µl ligand stock ([3H]-SCH 58261

for A_{2a}, [3H]- DPCPX for A_1). Add 100 µl of diluted membranes containing the appropriate receptor. Mix. Incubate at room temperature for 90 minutes. Harvest using a Brandel cell harvester onto Packard GF/B filter plates. Add 45 µl Microscint 20 (Packard), and count using the Packard TopCount Microscintillation Counter. Determine IC_{50} values by fitting the displacement curves using an iterative curve fitting program (Excel). Determine Ki values using the Cheng-Prusoff equation.

Haloperidol-induced catalepsy in the rat

Male Sprague-Dawley rats (Charles River, Calco, Italy) weighing 175-200 g are used. The cataleptic state is induced by the subcutaneous administration of the dopamine receptor antagonist haloperidol (1 mg/kg, sc), 90 min before testing the animals on the vertical grid test. For this test, the rats are placed on the wire mesh cover of a 25x43 plexiglass cage placed at an angle of about 70 degrees with the bench table. The rat is placed on the grid with all four legs abducted and extended ("frog posture"). The use of such an unnatural posture is essential for the specificity of this test for catalepsy. The time span from placement of the paws until the first complete removal of one paw (*decent latency*) is measured maximally for 120 sec.

The selective A_{2A} adenosine antagonists under evaluation are administered orally at doses ranging between 0.03 and 3 mg/kg, 1 and 4 h before scoring the animals.

In separate experiments, the anticataleptic effects of the reference compound, L-DOPA (25, 50 and 100 mg/kg, ip), were determined.

6-OHDA Lesion of the Middle Forebrain Bundle in Rats

Adult male Sprague-Dowley rats (Charles River, Calco, Como, Italy), weighing 275-300 g, are used in all experiments. The rats are housed in groups of 4 per cage, with free access to food and water, under controlled temperature and 12 hour light/ dark cycle. The day before the surgery the rats are fasted over night with water *ad libitum.*

Unilateral 6-hydroxydopamine (6-OHDA) lesion of the middle forebrain bundle is performed according to the method described in Ungerstedt et al, *Brian Research, 24* (1970), p. 485-493, and Ungerstedt, *Eur. J. Pharmacol., 5* (1968), p. 107-110, with minor changes. Briefly, the animals are anaesthetized with chloral hydrate (400 mg/kg, ip) and treated with desipramine (10 mpk, ip) 30 min prior to 6-OHDA injection in order to block the uptake of the toxin by the noradrenergic terminals. Then, the animals are placed in a stereotaxic frame. The skin over the skull is reflected and the stereotaxic coordinates (-2.2 posterior from bregma (AP), +1.5 lateral from bregma (ML), 7.8 ventral from dura (DV) are taken, according to the atlas of Pellegrino et al (Pellegrino L.J., Pellegrino A.S. and Cushman A.J., A Stereotaxic Atlas of the Rat Brain, 1979, New York: Plenum Press). A burr hole is then placed in the skull over

the lesion site and a needle, attached to a Hamilton syringe, is lowered into the left MFB. Then 8 μg 6-OHDA-HCl is dissolved in 4 μl of saline with 0.05% ascorbic acid as antioxidant, and infused at the constant flow rate of 1 μl /1 min using an infusion pump. The needle is withdrawn after additional 5 min and the surgical wound is closed and the animals left to recover for 2 weeks.

Two weeks after the lesion the rats are administered with L-DOPA (50 mg/kg, ip) plus Benserazide (25 mg/kg, ip) and selected on the basis of the number of full contralateral turns quantified in the 2 h testing period by automated rotameters (*priming test*). Any rat not showing at least 200 complete turns /2h is not included in the study.

Selected rats receive the test drug 3 days after the priming test (maximal dopamine receptor supersensitivity). The new A_{2A} receptor antagonists are administered orally at dose levels ranging between 0.1 and 3 mg/kg at different time points (i.e., 1, 6, 12 h) before the injection of a subthreshold dose of L-DOPA (4 mpk, ip) plus benserazide (4 mpk, ip) and the evaluation of turning behavior.

In the binding assay, adenosine A_{2a} receptor antagonists for use in the present invention preferably show A_{2a} Ki vaules of 0.3 to 100 nM, with preferred compounds showing Ki values between 0.3 and 5.0 nM.

Selectivity is determined by dividing Ki for A_1 receptor by Ki for A_{2a} receptor. Preferred compounds of the invention have a selectivity ranging from about 100 to about 2000.

Preferred compounds showed a 50-75% decrease in descent latency when tested orally at 1 mg/kg for anti-cataleptic activity in rats.

In the 6-OHDA lesion test, rats dosed orally with 1 mg/kg of the preferred compounds performed 170-440 turns in the two-hour assay period.

In the haloperidol-induced catalepsy test, a combination of sub-threshold amount of a compound of formula I and a sub-threshold amount of L-DOPA showed a significant inhibition of the catalepsy, indicating a synergistic effect. In the 6-OHDA lesion test, test animals administered a combination of a compound of formula I and a sub-threshold amount of L-DOPA demonstrated significantly higher (6-fold) contralateral turning.

Depression and anxiety are measure by the following tests, wherein immobility is an indication of depression.

Mouse tail suspension test

The tail suspension test is based on the observation that a mouse suspended by the tail shows alternate periods of agitation and immobility. The mouse, acoustically and visually isolated, is hung on the hook by an adhesive tape placed 20 mm from the extremity of its tail and it is kept 150 mm away from the nearest object.

The duration of immobility is recorded for 6 min. The sum of immobility periods (duration of immobility) is measured by an observer who was unaware of the drug treatments. Each mouse is used only once for each experimental session.

Mouse and rat forced swim test

Mouse: In the forced swimming test, mice are dropped individually into glass cylinders (height: 25 cm, diameter: 10 cm) containing 10 cm water, maintained at 25°C, and left there for 6 min. A mouse is judged to be immobile when it floats in an upright position, and makes only small movements to keep its head above water. The duration of immobility is recorded during the last 4-min of the 6-min testing period. The sum of immobility periods (duration of immobility) is measured by an observer who is unaware of the drug treatments. Each mouse is used only once for each experimental session.

Rat: Rat is placed in a cylinder 40 cm high and 18 cm in diameter containing 20 cm of water at 25°C. The animal is left to swim in the water for 15 min before being removed, allowed to dry beside a heated enclosure and returned to its home cage. Twenty-four h later, the animal is exposed again to the conditions outlined above and the total immobility time during a 5-min period recorded (test session). Furthermore, we also measure the active behavior of the animal as the time spent in climbing. Drugs are given 3 times before testing: 24, 5 and 1 h. In each test the measurements are always made under blind conditions.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compounds are administered orally.

Preferably, when the combination of drugs is administered in a single pharmaceutical composition, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of each active component, e.g., an amount effective to achieve the desired purpose.

The amount and frequency of administration of the compounds in the combination of this invention will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The combination of drugs can be administered individually, either simultaneously or sequentially, in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. Different drugs can be administered in different dosage forms. When used in combination, the dosage levels of the individual components are preferably lower than the recommended individual dosages because of the advantageous effect of the combination.

The quantity of adenosine A_{2a} receptor antagonist in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg, according to the particular application. A typical recommended dosage regimen for an adenosine A_{2a} receptor antagonist is oral administration of from 10 mg to 2000 mg/day, preferably 10 to 1000 mg/day, in two to four divided doses to treat depression or anxiety-related disorders.

The doses and dosage regimens of the antidepressant and anxiolytic components of the combination will be determined by the attending clinician in view of the approved doses and dosage regimen known in the art, e.g., in the package insert or other published information, taking into consideration the age, sex and condition of the patient and the severity of the disease.

When the adenosine A_{2a} receptor antagonist and antidepressant or anxiolytic are to be administered separately, they can be provided in a kit comprising in a single package, one container comprising an adenosine A_{2a} receptor antagonist in a pharmaceutically acceptable carrier, and a separate container comprising an antidepressant or anxiolytic in a pharmaceutically acceptable carrier, with the adenosine A_{2a} receptor antagonist and the antidepressant or anxiolytic agent being present in an amount such that the combination is effective to treat depression or anxiety-related disorders. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms (i.e., tablet and capsule).

The following are examples of pharmaceutical dosage forms suitable for the present invention. Those skilled in the art will recognize that dosage forms are suitable for single actives (i.e. "Active" is an A_{2a}receptor antagonist or an antidepressant or an anxiolytic), or can contain both components (ie, "Active" comprises both an adenosine A_{2a} receptor antagonist and an antidepressant or anxiolytic). The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and

mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

1. The use of a combination of an adenosine A_{2A} antagonist and an antidepressant or an anxiolytic for treating depression or anxiety-related disorders.

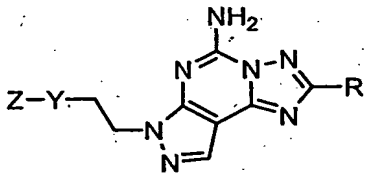
2. The use of claim 1 wherein the adenosine A_{2a} receptor antagonist is selected from those described in formulas I, II, III, IVA, IVB, V, VI, VII, VIII and IX as disclosed in the specification.

3. The use of claim 1 wherein the antidepressant is selected from selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and mixed serotonin/norepinephrine reuptake inhibitors.

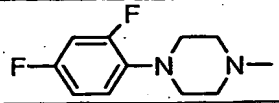
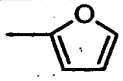
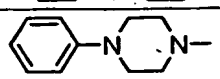
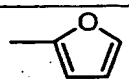
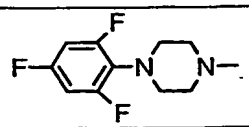
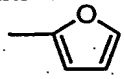
4. The use of claim 2 wherein the antidepressant is selected from fluoxetine, sertraline, paroxetine, citalopram, mirtazepine, fluvoxamine, reboxetine, desipramine, amitriptyline, nortriptyline, imipramine, venlafaxine, buproprion, nefazodone and milnacipran and the anxiolytic is selected from alprazolam, buspirone, lorazepam, diazepam, clonazepam, doxepin, chlordiazepoxide and meprobamate.

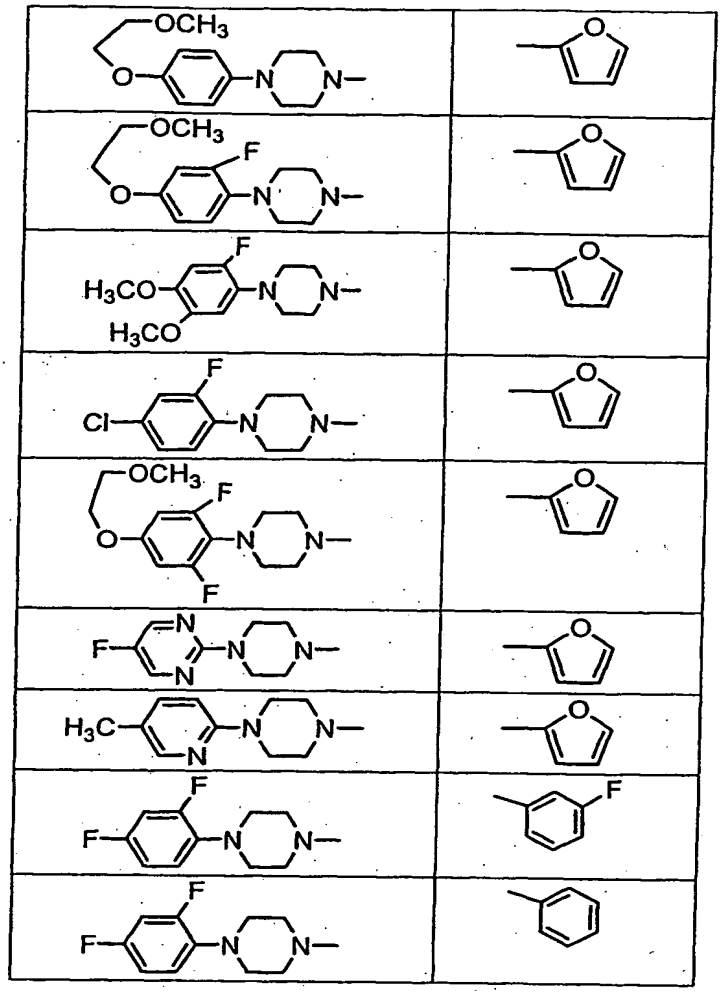
5. The use of claim 4 wherein the adenosine A_{2a} receptor antagonist is selected from those described by formula I as disclosed in the specification.

6. The use of claim 6 wherein the adenosine A_{2a} receptor antagonist is represented by the formula



wherein R and Z-Y are as defined in the following table:

Z-Y-	R
	
	
	



7. A pharmaceutical composition comprising a therapeutically effective amount of a combination of an adenosine A_{2a} receptor antagonist and an antidepressant or an anxiolytic in a pharmaceutically acceptable carrier.

8. The composition of claim 7 wherein the adenosine A_{2a} receptor antagonist is selected from those described in formulas I, II, III, IVA, IVB, V, VI, VII, VIII and IX as disclosed in the specification.

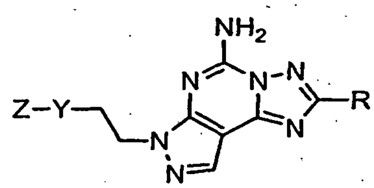
9. The composition of claim 7 wherein the antidepressant is selected from selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and mixed serotonin/norepinephrine reuptake inhibitors.

10. The composition of claim 8 wherein the antidepressant is selected from fluoxetine, sertraline, paroxetine, citalopram, mirtazapine, fluvoxamine, reboxetine, desipramine, amitriptyline, nortriptyline, imipramine, venlaflaxine, buproprion,

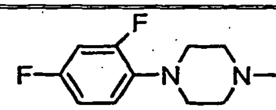
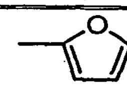
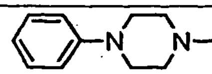
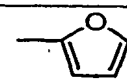
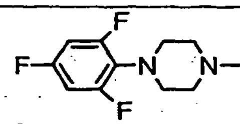
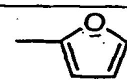
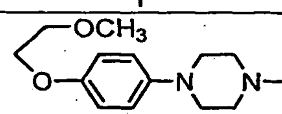
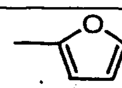
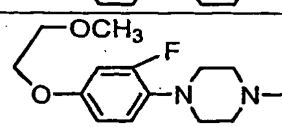
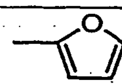
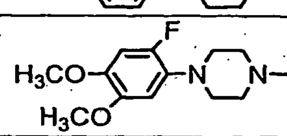
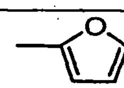
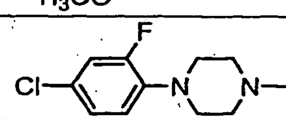
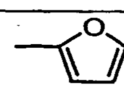
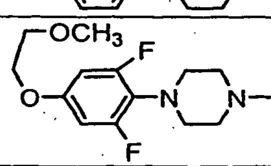
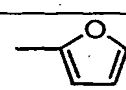
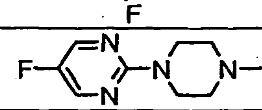
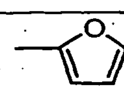
nefazodone and milnacipran and the anxiolytic is selected from alprazolam, buspirone, lorazepam, diazepam, clonazepam, doxepin, chlordiazepoxide and meprobamate.

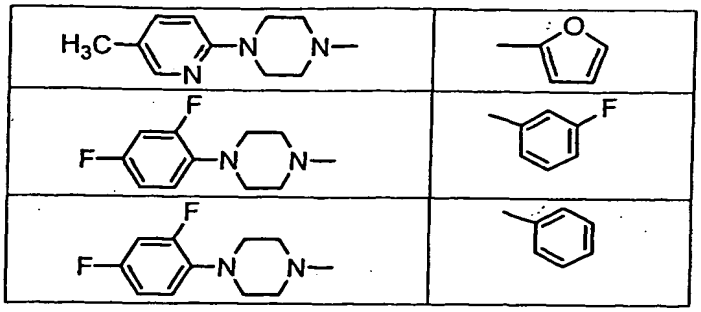
11. The composition of claim 10 wherein the adenosine A_{2a} receptor antagonist is selected from those described by formula I as disclosed in the specification.

12. The composition of claim 11 wherein the adenosine A_{2a} receptor antagonist is represented by the formula



wherein R and Z-Y are as defined in the following table:

Z-Y-	R
	
	
	
	
	
	
	
	
	



13. A kit comprising in a single package, one container comprising an adenosine A_{2a} receptor antagonist in a pharmaceutically acceptable carrier, and a separate container comprising an antidepressant in pharmaceutically acceptable carrier or an anxiolytic in a pharmaceutically acceptable carrier, with the adenosine A_{2a} receptor antagonist and the antidepressant or anxiolytic agent being present in amounts such that the combination is effective to treat depression or anxiety-related disorders.

INTERNATIONAL SEARCH REPORT

Internatio pplication No
PCT/US 02/28865

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519 A61K31/53 A61P25/22 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, CANCERLIT, PASCAL, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EL YACOUBI MALIKA ET AL: "Adenosine A2A receptor antagonists are potential antidepressants: Evidence based on pharmacology and A2A receptor knockout mice." BRITISH JOURNAL OF PHARMACOLOGY, vol. 134, no. 1, September 2001 (2001-09), pages 68-77, XP009004386 ISSN: 0007-1188 abstract	1-13
X	EP 1 116 722 A (KYOWA HAKKO KOGYO KK) 18 July 2001 (2001-07-18) page 2, paragraph 5	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2003	05/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sindel, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ial application No.
PCT/US 02/28865

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13

Present claims 1-13 relate to an extremely large number of possible compounds and products. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 2 and 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US 02/28865

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1116722 A	18-07-2001	AU 5757999 A	10-04-2000
		BR 9914040 A	15-01-2002
		CA 2344828 A1	30-03-2000
		EP 1116722 A1	18-07-2001
		HU 0103921 A2	29-04-2002
		NO 20011417 A	21-05-2001
		CN 1328560 T	26-12-2001
		WO 0017201 A1	30-03-2000